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REVIEW ARTICLE

Protein Misfolding in Neurodegenerative Disorders: Mechanisms, Consequences, and Emerging Therapies

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ABSTRACT: Protein misfolding occurs when the 3D protein structures fold incorrectly, resulting in accumulation and formation of toxic aggregates. Protein misfolding plays a crucial role in the pathogenesis of many neurodegenerative diseases. This review will examine the causes of protein misfolding, its relation to neurological diseases, and possible cellular and therapeutic treatments. The cellular treatment includes a dive into the ubiquitin-proteasome system and macroautophagy for protein quality control, as well as the use of chaperones— molecular, chemical, and pharmacological— to reduce misfolded protein levels and aggregate accumulation. The therapeutic treatments consider the antibodies developed for Alzheimer's and Parkinson's disease, and explore which ones worked and the reason why some of them failed. The paper also highlights the importance of research efforts in developing and accelerating these therapeutic strategies. Treating these disorders is extremely important because they can severely impact the lives of those who deal with them. Understanding the mechanisms and the treatments to protein misfolding can help us improve patients' lives and pave a clearer path for how to deal with these disorders. This review aims to provide a deep understanding of protein misfolding associated with neurological disorders, and promising treatments.

KEYWORDS: Cellular and Molecular Biology, Genetics, Neurodegenerative diseases, Protein misfolding, Toxic aggregates, Amyloid-beta, Tau protein, Alzheimer's Disease.

Introduction

The precise folding of proteins is vital for maintaining the balance of life. If this process contains an error, it can trigger a cascade of negative effects that can have an impact on neurological processes and functions. Protein conformation is crucial to the manner in which it functions. Any structural change to the shape of a protein, even changes that involve folding, can cause it to function in a different way, or even ensure that it is non-functional.[1] This can result in accumulation of toxic aggregates, which can have negative effects on the pathogenesis of neurodegenerative diseases. Protein synthesis, folding, and degradation needs to be properly balanced, which is essential to its biological activity. Additionally, the abundance of each protein must be carefully regulated to preserve proteome integrity and cellular health. Linear amino acid sequences of synthesized polypeptide chains contain information that makes up the structure of a protein. Amino acids can adopt a wide range of conformations, which are only often stable under certain conditions. If there is any abnormality in these conditions, errors can result that can potentially lead to misfolded structures and off pathway aggregates.[2]

Protein misfolding is not an error that affects only cellular function, but it can also affect the pathogenesis of neurodegenerative diseases. Buildup of these aggregates can be linked to numerous neurological diseases, such as Alzheimer's disease and Parkinson's disease, which are diseases that affect older people in society, and are caused due to cellular toxicity–which, through research, has shown to result from misfolding proteins.[2] These such diseases have a great impact on people worldwide. With more than 3 billion people around the world living with a neurological disorder in 2021,[27] the prevalence of these diseases is extremely high, prompting the need for research behind what could cause the neurodegenerative disorders.

Given the impact that protein misfolding has on health, it is crucial to understand the mechanisms behind protein misfolding. Gaining insight into this is key in designing therapeutic strategies to target protein aggregation and accumulation. This paper aims to review evidence that has already been collected, so that further research can be conducted to reach one step closer to develop possible treatments. By diving into how exactly protein misfolding can occur, linking it to neurodegenerative diseases, and understanding both cellular and therapeutic treatments, scientists can make great strides in the further discovery of these misfolded protein neurodegenerative diseases.

Discussion

Mechanisms of Protein Misfolding:

Protein synthesis is defined as the process of creating proteins that are used within the body. Proteins are a larger subunit of amino acids, which are linked by peptide bonds. There are four protein structures: primary, secondary, tertiary, and quaternary.[4] The use of different amino acid combinations is crucial to the structure and intended function of the protein. Protein chains are folded and connected by non-covalent bonds, which are weak, and easy to break apart. However, the non-covalent bonds are able to work together to stabilize the protein.[5] The strength of the non-covalent bonds—which are either ionic or hydrogen— determine the stability.[5] There are four types

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of protein structure. The primary structure is defined by the amino acid sequence that forms a polypeptide chain. The secondary structure is the chain that manipulates its shape to form either an alpha helix or a beta-pleated sheet. The tertiary structure is a three-dimensional structure that is held together by various types of bonds, and the quaternary structure is a protein compound that is formed of more than one polypeptide chain.[5] How are these proteins created? Protein synthesis occurs when an 80S ribosome, a Met-tRNA (initiator methionyl-transfer RNA) and an mRNA (messenger RNA), all combine so that codon-anticodon base pair matching occurs.[3] This process synthesizes amino acids, which form a chain that creates proteins and can be one of the four different types of structures.

The function of a protein can only be carried out if the protein has a certain structure, or conformation, that is attained by the manner in which it is folded. This is true for any proteins in the body, and does not pertain to specifically neurodegenerative diseases. Protein structure is crucial for the manner in which it functions in all organisms. Any change in that structure, whether it is misfolded, even slightly, or missing a part, can result in it deactivating, or activating to perform a different function. This can be negative, as it can have a harmful result for the organism.[21] Specifically, in misfolded protein structures, there are larger amounts of the beta structure as compared to the regular (native) structure. These beta fragment proteins form amyloid fibrils, which are present in people with neurodegenerative diseases. Some conditions, such as extreme pH, the composition of the pH, and high pressure, can result in globular proteins becoming the amyloid structure, even though these conditions are rare.[6]

Małolepsza, Boniecki, and Kolinski led a study to determine how prion disease (misfolded protein disease) can be propagated. They researched the possibility that involves two interacting protein molecules. In this experiment, one was in the metastable (slightly unstable) form, while the other was stable. They found that, when the proteins interacted, instead of folding to the normal alpha helix form, it folded into a beta conformation, which was toxic. These results show how misfolded protein accumulation can occur. A second trial was run that tested how long it took for the beta form to change their shape, but it remained stable for a long time. The three trials explained how protein structures can misfold when in proximity to other misfolded proteins, and how this can accumulate. The fact that the misfolded structure remained stable for a long time additionally indicates the implications of the misfolded structures, as they are able to remain unchanged and can therefore lead to aggregation. This figure (Figure 1) depicts how the native alpha helix form of the protein became a misfolded beta protein when it was in the presence of another misfolded beta structure. It highlights how those misfolded structures can be created and accumulated.[6]

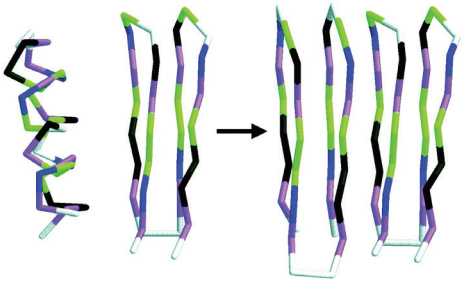

Figure 1: Structure on the far left is an example of the alpha helix protein structure.[6] This is the native structure and the non-toxic protein formation. The structure on the right of the alpha helix is a beta-pleated sheet, and is the unstable form that is the misfolded structure. The arrow describes the reaction that occurs when they are placed next to each other, and the side-by-side beta-pleated sheets are the result of the interaction between the alpha helix, or the native structure, and the toxic beta sheet.[6]

Protein misfolding is caused by incorrect folding of proteins into beta-sheet aggregated structures. From these structures, oligomers, proto-fibrils, and fibrils are accumulated, which create amyloid deposits in tissues. These aggregates can look different and play a role in the pathogenesis of different diseases, and this is mainly based on the way that it is misfolded. This is caused due to a plethora of reasons including but not limited to: gene sequence mutations that result in a protein that cannot form the native (normal) folding, transcription or translational process problems which results in proteins that are unable to fold in the manner that is needed, and failure of folding machinery. It can also be due to the post-translational modification errors, protein misfolding by seeding mechanisms, and finally environmental changes— like high pH or temp, which can cause denaturation, and affect the protein structure, affecting its function.[7] Protein misfolding is an error to the normal process of protein synthesis and can have negative effects on people.

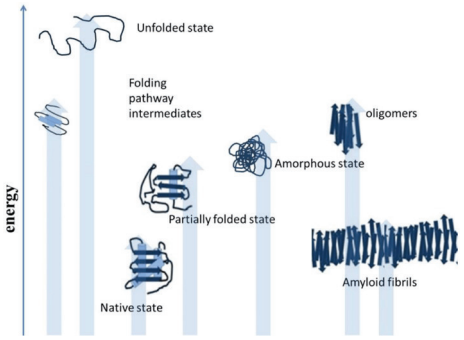

Figure 2: The figure describes the energy of differing protein structures. It explains how proteins that diverge from the native, intended structure of protein can form into misfolded protein structures. It includes different protein structures, such as native, partially folded, amyloid fibrils, amorphous state, oligomers, and unfolded state, and their correlation with energy.

The above figure (Figure 2) is a depiction of how these misfolded protein structures can manifest themselves in a plethora of forms, all of which have the potential to be toxic for the cells. There are some proteins that are more prone to misfolding and degradation, such as amyloid beta proteins, and some that are not. Native structures of proteins are the most stable and has minimum energy when the conformation is fixed. This means that, as the energy decreases, protein structures become more

ordered and closer to the native state.[25] The figure (Figure 2) we can see that the increase in energy leads to different intermediates of misfolded proteins, with the highest being the completely unfolded state.

Neurodegenerative Diseases Associated with Protein Misfolding:

Misfolded proteins, through research, are shown to possibly play a critical role in the pathogenesis of neurodegenerative diseases. This is because misfolded proteins can cause cellular toxicity, which can lead to these types of diseases. "Loss-of-function" diseases are one type of disease that can stem from prions (which are misfolded proteins) that are metastable–slightly unstable–, and this can result in proteins being prone to degradation. The other type of disease is "toxic gain-of-function diseases", which is where metastable proteins are aggregated and result in cellular toxicity.[2] These diseases can be genetic and heritable, but in reality, are often a result of a "decline in the capacity of the proteostasis network."[2]

This decline in function is created by the misfolded protein aggregates. This occurs when misfolded proteins mistakenly make contact between their hydrophobic amino acid areas and the solvent, which creates the beta-sheet structure aggregates. What would normally act within the molecule for stabilization, acts between molecules when they form aggregates. These amyloid folding proteins form deposits in extracellular space in the nervous system. The proteins associated with those are related with specific diseases and have an "intrinsic ability" to be able to aggregate in the beta-sheet structure.[2]

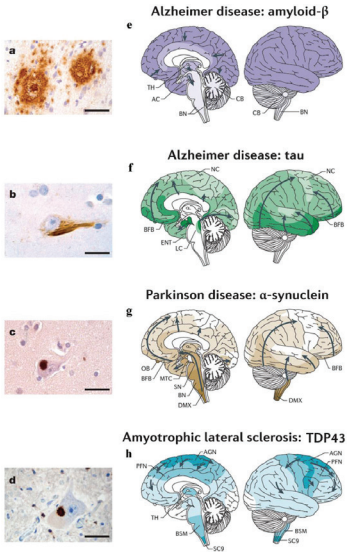

Figure 3: From a separate review paper published in Frontiers, this figure provides a clear example of some of the proteins that are associated with certain diseases. For Alzheimer's disease, it is the amyloid-beta and tau proteins, for Parkinson's disease it is the a-synuclein protein, and for amyotrophic lateral sclerosis, it is the TDP43 protein. Misfolded protein aggregates for any of these proteins can contribute to the development of any of these neurological diseases. The images on the left depict an example of the progression patterns, while the figures on the right indicate the protein that is found to be associated with the disease, as well as the area of the brain it affects. [14]

- ***Alzheimer's Disease:***

Alzheimer's disease, a neurological disorder associated with memory loss, is one of the diseases that is thought to be connected to misfolded proteins. This is extremely controversial due to the fact that there are various possible causes and no definite one. However, the research behind misfolded proteins and its association with this disease has shown to be promising in providing information about the cause. It says that overproduction of the amyloid beta peptide can create amyloid plaques. These plaques of misfolded proteins can slow down communication between neurons, and can lead to behavioral symptoms and difficulties in Alzheimer's disease.[8] The misfolded proteins of beta-amyloid and TAU proteins can create oligomers and fibrils that interfere with healthy cell function, which can result in death of neurons that lead to the pathogenesis of Alzheimer's disease.[11] Tau proteins can be found in microtubules in the axons of the neurons. They serve to stabilize them to help them function. In the space between the neurons, smaller versions of tau proteins, called oligomers, exist. If these oligomers accumulate, they can disrupt communication between neurons. They form structures called neurofibrillary tangles, which damage axons and disrupt signals. Spreading through areas of the brain, it affects learning and memory, as well as the overall pathogenesis of the disease. Accumulation of these misfolded protein structures can contribute to the development of Alzheimer's.[12] Another form of misfolded protein that can cause Alzheimer's is error in the structure of beta-amyloid protein. The misfolded structure of this protein is created due to a gene called presenilin 1, which has a mutation where few nucleotides are changed. This causes the production of a defective PSEN1 protein, which affects the way that the gamma secretase protein complex functions. This causes it to alter the processing of the amyloid precursor protein, leading to a longer and misfolded version of the amyloid beta peptide, which is toxic. They clump together and form amyloid plaques, which causes the death of neurons and progresses the development of Alzheimer's Disease.[9] Mutations in the PSEN 2 gene can also result in the overproduction of the amyloid beta peptide, which is another way that the amyloid plaques can be formed, leading to pathogenesis of Alzheimer's.[10]

- ***Parkinson's Disease:***

Another neurodegenerative disease that is often associated with misfolded proteins is Parkinson's disease. Research in this disease has revealed that the main protein that may possibly contribute to the disease is a-synuclein. A-synuclein is a protein in the brain that has currently unknown physiological functions, but has been found to be linked with processes occurring near the membrane and the presynaptic terminal.[26] The accumulation of misfolded and aggregated α-synuclein in the brain can disrupt cellular function and can lead to neurodegeneration. An experiment conducted at UTHealth Houston, involved a cross-sectional analysis of the a-synuclein seed amplification assay to evaluate its sensitivity and specificity for diagnosing Parkinson's disease.[22] This was relevant as it can help identify individuals that have the disease. They also assessed molecular diversity and tried to identify individuals at risk based on clinical and genetic features. The results found that the a-synuclein seed amplification assay (SAA) had a sensitivity of 87.7% and specificity of 96.3% for distin-

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guishing Parkinson's disease patients from healthy controls.[22] Sensitivity was at different levels with different variations of the disease, being at its highest in sporadic Parkinson's disease patients with olfactory struggles and lowest in LRRK2 Parkinson's disease.[22] Additionally, 86% of participants with rapid eye movement sleep behavior disorder (RBD) or hyposmia (prodromal Parkinson's) had positive α-synuclein SAA results.[22] This had greater implications in understanding more about the disease. It showed that the a-synuclein SAA can identify subgroups of Parkinson's disease and act as a biomarker. It can also highlight the diversity among the patients. The study provides important implications for early diagnosis and clinical trials of Parkinson's.[22] It shows how, even though the a-synuclein protein misfold contributes to the pathogenesis of the disease, SAA can be used to diagnose the variation and at-risk individuals to help with treatment.

Cellular Approaches for Dealing with Misfolded Proteins:

Mammalian cells have many proteolytic systems that are used to manage misfolded proteins. As explored earlier, misfolded proteins can create aggregates, which can lead to cellular toxicity and eventually neuro-degenerative diseases. For this reason, cells have developed three primary systems to maintain protein homeostasis. These systems are the ubiquitin proteasome system, chaperone-mediated autophagy, and macroautophagy.[20]

- ***Protein Quality Control Systems:***

The ubiquitin proteasome system is the first method to manage misfolded proteins. This proteolytic pathway involves tagging proteins with ubiquitin. This signals them for degradation. First, ubiquitin is activated by an E1 enzyme, which forms a thioester bond with the C-terminal glycine of ubiquitin. Then, the activated ubiquitin is transferred to E2, a ubiquitin-conjugating enzyme.[20] The ubiquitin ligase, E3, then recognizes and meditates the transfer from E2 to the lysine residues of the target substrate.[20] Once there is a chain of four or more ubiquitin at lysine, the substrates can be delivered to the 26S proteasome, which is a structure that degrades misfolded proteins.[20] A particle on the proteasome unfolds the ubiquitin substrate and cleaves it into small peptides. This process is extremely important for degrading misfolded proteins.[20]

Chaperone-mediated autophagy is the next system that specifically targets misfolded proteins. The proteins that they target are ones that have a specific degradation signal, the KFERQ motif.[20] This motif is recognized by the chaperone Hsc70, which guides the delivery of the protein to a protein in the lysosomal membrane called LAMP-2A.[20] After it binds to this protein, it is unfolded and moved into the lysosomal lumen, where it is degraded by biochemical enzymes in the lysosomal lumen to be converted to amino acids. This is a step that helps allow for the clearance of misfolded proteins.[20]

Macroautophagy is the final cellular form of protein quality control. It is responsible for larger aggregates of misfolded proteins. In this process, there is a formation of double-membrane structures called autophagosomes, which is where the misfolded proteins are delivered to by the autophagic adaptor p62.[20] P62 has two domains that help with this; a ubiquitin association domain that interacts with the polyubiquitin chain of misfolded protein and a PB1 domain that controls self-aggregation.[20] These domains work together to form cargo-p62 complexes which are delivered to autophagic vacuoles.[20] P62 is able to reduce the toxicity of an oligomeric misfolded protein by delivering it to the autophagic vacuoles.[20] Once they are loaded to the autophagosomes, they are fused with the lysosomes, making autolysosomes, in which the cargo-p62 complexes with misfolded proteins are degraded by lysosomal hydrolases. This pathway is very important for clearing aggregated forms of proteins associated with neurodegenerative diseases.[20]

- ***Chaperones:***

There are also other cellular approaches for detailing with misfolded proteins. Chaperones are specialized proteins that are designed to help to manage protein folding. There are three main categories of chaperones, molecular, chemical, and pharmacological chaperones, with each playing a distinct role in protein quality control and folding.

Molecular chaperones are proteins that help with the proper folding of polypeptides and prevent misfolding and protein aggregation. They interact with proteins during synthesis and translocation to help ensure that they form in the correct and functional 3D structure. They recognize non-native conformations and help refold misfolded proteins or direct them to the ubiquitin-proteasome system where they can undergo degradation.[15-17] They can help enhance folding efficiency and prevent toxic aggregate formation. There are different types of chaperones. Some of them include heat shock proteins, which are stress-induced and upregulated when there are cellular changes. For example, oxidative stress can lead to more misfolded proteins, so expressing the chaperones can help reduce the effects of the cellular changes and conduct proper protein folding.[15-17] Some other chaperones are associated with the endoplasmic reticulum, which is where the proteins are made, and are responsible for recognizing and keeping misfolded proteins, only allowing correct proteins to go and perform their function.[15-17]

There are also chemical chaperones which help in protein folding by creating a more favorable environment for proper conformation. They can stabilize proteins by altering the cellular conditions, such as maintaining optimal states and solubility. The last type of chaperone are pharmacological chaperones, which are smaller molecules that bind to misfolding proteins and stabilize their functional conformations. They can enhance the stability and fix the activity of misfolded proteins, helping to regulate correct function. These chaperones are created to target specific misfolded proteins associated with diseases, making them a promising therapeutic approach for protein misfolding neurological disorders.[15-17]

Therapeutic Approaches for Dealing with Alzheimer's Disease and Parkinson's Disease:

Currently, scientists in the field are working on utilizing antibodies to try and treat these neurodegenerative disorders that result from protein misfolding. These antibodies work specifically to target the misfolded proteins, and are aimed to prevent further development of such neurological diseases. Since they

are currently being developed, it is not used to eradicate the disease entirely, but rather prevent further pathogenesis and attempt to reduce symptoms that are a direct result of the misfolded proteins involved in the disease. The primary antibodies that have been developed recently are created for treating Alzheimer's Disease and Parkinson's disease. Monoclonal antibodies, which are a laboratory made clone of the body's antibodies used to treat diseases, can be designed to target specific proteins. In this case, the monoclonal proteins can be used to target the proteins that are involved with certain neurological disorders. In the case of Alzheimer's, antibodies specifically target the amyloid-beta and tau proteins by preventing accumulation and increasing clearance. In Parkinson's, the a-synuclein protein is targeted.[19]

Below is a table (Table 1) that explains the approved antibodies for Alzheimer's. These specific antibodies target the amyloid beta aggregates, and work on the clearance of them. These are successful antibodies that have been used as a potential treatment for Alzheimer's disease. In this case, the antibodies mainly serve as a treatment by blocking the further aggregation of amyloid beta structures, causing the accumulation to slow down.[19]

Table 1: (Reprints with permission from Huang *et al.* 2023.[19])

Name	Synonyms	Company	Target	Therapy type	Approval status
Aduhelm	Aducanumab, BIIB037	Biogen, Neurimmune	Aβ aggregates	Immunotherapy (passive)	Accelerated approval
Leqembi	Lecanemab-irmb, BAN2401	BioArctic AB, Biogen, Eisai	Aβ protofibrils	Immunotherapy (passive)	Full approval
Donanemab	N3pG-Aβ Monoclonal Antibody, LY3002813	Eli Lilly & Co	Aβ aggregates	Immunotherapy (passive)	Application for full approval

The following table (Table 2) also discusses antibodies but focuses on antibodies that are not yet approved and are still going through the FDA approval process. These monoclonal antibodies also work in a similar way by either recognizing the amyloid beta protein or signaling the blockage of further aggregation.[19]

Table 2: (Reprints with permission from Huang *et al.* 2023.[19])

Aducanumab (EMBARK)	Biogen, Neurimmune	BIIB037	Immunotherapy (passive)	NCT04241068	Active, not recruiting
Aducanumab (ENVISION)			Immunotherapy (passive)	NCT05310071	Recruiting
Donanemab (TRAILBLAZER-ALZ 2)	Eli Lilly & Co	N3pG-Aβ Monoclonal Antibody	Immunotherapy (passive)	NCT04437511	Active, not recruiting
Donanemab (TRAILBLAZER-ALZ 3)			Immunotherapy (passive)	NCT05026866	Recruiting
Donanemab/Aducanumab (TRAILBLAZER-ALZ 4)			Immunotherapy (passive)	NCT05108922	Active, not recruiting
Donanemab (TRAILBLAZER-ALZ 5)			Immunotherapy (passive)	NCT05508789	Recruiting
Donanemab (TRAILBLAZER-ALZ 6)			Immunotherapy (passive)	NCT05738486	Recruiting

However, there has been a lot of failure in this field, due to a multitude of reasons. The main reason is due to the fact that there was a lack of drug selectivity for the oligomeric amyloid beta proteins. Additionally, antibodies as a treatment have failed on some patients in the advanced state of the disease and patients with sporadic Alzheimer's rather than autosomal dominant Alzheimer's.[23] The failure of antibodies can also be attributed to how the drugs were tested in those who did not have the amyloid beta biomarker present, which is ineffective because the drugs are specifically designed to target this protein. If the antibody is created to specifically affect a protein that is considered to be connected to Alzhimer's it is important that the protein is present, so that efficient treatment can be conducted. Furthermore, previous studies have indicated that failures of tau antibodies can be linked to the fact that the drugs may depend on targeting the precise region of the tau protein. If the antibody does not bind to the correct region of the tau protein, they may not be able to successfully neutralize tau's effects. The paper done by Imbimbo *et al.* argues that, rather than focuses on how to reduce soluble amyloid beta and tau levels, it would be more beneficial to concentrate on how they form deposits in the first place, so that the process can be inhibited.[23] This could be effective because targeting the process of the primary creation of deposits can serve to be more efficient that reducing amounts later on.

Another major setback for the therapeutic field is a current controversy in the field. A paper, written by Lesné *et al* was revolutionary to the research in the field at that time.[18] It provided strong evidence that the amyloid beta protein was the root cause of Alzheimer's disease, including "data" involving mice trials. This was a major stepping stone in neurodegenerative disease research, because before this, researchers didn't know the true cause of Alzheimer's disease and believed that this provided the reason and evidence. The article was cited 2355 times, but suddenly retracted in June 2024. They found that the paper included doctored images about the data, which leads some to believe that it was manipulated.[24] This has the potential to set the field back by as much as 15 years, because it was the building block for so much research done since then. Due to this setback, it may be difficult to collect data and develop therapeutic strategies because it was based on findings of this paper. As the paper drew definitive conclusions that the amyloid protein was involved, efforts increased to target this specific protein in Alzhimer's treatment. However, as evidence has shown that, while the amyloid protein can relate to Alzhimer's pathogenesis, it is crucial to continue to research. For further therapies, it is essential to consider other proteins that could be involved in Alzhiemers, and how we can alter the mechanism of action in the antibodies to target treatment.

■ Conclusion

This review paper synthesizes crucial information about the neurological disorders that are associated with protein misfolding. It explores the mechanisms behind protein misfolding. Specifically, it examines its causes and its implications. It also explains the link between these misfolded proteins and neurodegenerative diseases. By highlighting both the tau proteins and amyloid beta proteins involved with Alzheimer's disease, as well as the a-synuclein protein in Parkinson's and the promising result of the SAA in early diagnosis, researchers can gain an understanding on the effect of misfolded protein

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aggregates on neurological disorders. Additionally, this paper explores both the cellular approaches of dealing with misfolded proteins— the ubiquitin proteasome system, chaperone-mediated autophagy, macroautophagy, and chaperones— and the therapeutic approaches—developed antibodies. This paper consolidates the vast amount of information on misfolded and cleverly touches on all key points of information necessary when wanting to learn about the interplay between misfolded proteins and neurodegenerative diseases. However, there is still a lot of information that is yet to be researched. Due to the extreme implications of protein misfolding, it is crucial to develop more research. While new therapeutic models and approaches are still being developed, the need for more research is vital in understanding more about possible treatments and the true mechanisms behind misfolded-protein-associated neurological diseases.

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